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Filed: November 4, 2003

REMARKS

With entry of the present amendment claims 1 to 11, 13, and 15 to 22 are pending. Claims 12 and 14 have been cancelled, and claims 15, 18, and 20 have been amended to better clarify the invention. In addition, claims 1, 17, and 18 have been amended to correct the spelling of analyzed/analyzing. The amended claims are supported by the specification and claims as filed. No new matter has been added.

No additional fees are believed due. However, the Director is hereby authorized to charge any deficit, or credit any overpayment, to Deposit Account No. 08-2525.

REJECTION OF CLAIMS 12 AND 14 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH AS NONENABLED

Claims 12 and 14 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled. While not acquiescing to the rejection, claims 12 and 14 have been cancelled, rendering this rejection moot.

REJECTION OF CLAIMS 15, 18, AND 20 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH AS INDEFINITE

Claims 15, 18, and 20 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. In particular, the office action states that claim 15 contains improper Markush language, the recitation of “with the help of base-line separation” in claim 18 is unclear, and that claim 18 lacks antecedent basis for the term “in body fluid” used in claim 20.

Applicants respectfully traverse this rejection for the following reasons.

Claim 15 has been amended as suggested by the Examiner to recite traditional Markush language and to depend from claim 1, as claim 14 has been cancelled.

Claim 18 has been amended to clarify step (f) by reciting that the amount of beta amyloid is determined by analyzing the peaks that can be separated from the base-line peak pattern. In other words, measuring the peaks associated with the natural and stable ¹⁵N isotopes in the beta amyloid sample.

Claim 20 has been amended to correct the spelling of the word “peptide” and to indicate that the beta amyloid content quantified is that in “the sample” of claim 18 as opposed strictly to “body fluid.”

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 1, 5 TO 13, 16, AND 17 UNDER 35 U.S.C. § 103 AS OBVIOUS OVER BOUGNERES ET AL IN VIEW OF KAMETANI ET AL.

Claims 1, 5 to 13, 16, and 17 stand rejected under 35 U.S.C. § 103 as obvious over Bougneres et al. in view of Kametani et al. In particular, the Office Action states that Bougneres et al. describes a method for quantifying palmitate by providing a source of palmitate, adding a defined amount of palmitate labeled with stable isotope (H² and/or C¹³), isolating the labeled and unlabeled palmitate, desalting the sample to be analyzed, analyzing the sample by mass spectroscopy, and determining the amount of palmitate present in the source. The Office Action further states that Kametani et al. describes a method for the semiquantitation of β -amyloid peptides from homogenized brain tissue in which a β -amyloid antibody is added, and the precipitated antibody- β -amyloid complex is analyzed using MALDI-TOF spectroscopy.

The Office Action admits that Bougneres et al. does not teach use of the method with β -amyloid; a method of isolating β -amyloid from a body fluid using protein chemistry and immunochemistry or from tissue using dissolution with solubilizing agents; the preparation for

analysis by mass spectroscopy using chemical reactions with flight enhancers, chemical fragmentation, and enzymatic digestion by a protease; a method of using MALDI-TOF spectroscopy; or a method wherein labeled β -amyloid has been either synthetically or recombinantly produced. However, it is alleged that one of ordinary skill would have been motivated to combine the methods of the references because he would have known that the GLC Mass Spectroscopy used by Bougneres et al. is not sensitive enough to detect the β -amyloid peptide of interest and that MALDI-TOF would be better suited for such detection. The rationale for combining the references is that one would have had a reasonable expectation of success in combining the two methods because each has been used individually.

Applicants respectfully traverse this rejection, first because the references are not properly combinable and second because, even if combined, the references do not teach or suggest the claimed invention. The references are not properly combinable because they relate to completely different types of assays to determine different parameters of different types samples. In particular, Bougneres et al. describes a multistep assay which includes adding a labeled palmitate as a standard to a sample containing unlabeled palmitate and then determining the amount of unlabeled palmitate in the sample using Mass Spec. In contrast, Kametani et al. uses immunoprecipitation to determine the relative amounts of one particular length polypeptide of β -amyloid as compared to one other specific length polypeptide of β -amyloid. Kametani et al. accomplishes this determination in a one step process by which a β -amyloid-antibody complex is formed and immunoprecipitated. Measurement of the precipitated β -amyloid-antibody complexes provides a ratio of two different forms of β -amyloid, β 1-42 and β 1-40.

Neither Bougneres et al. nor the instant claims are directed to immunoprecipitation. Neither involves the formation of an antibody complex to determine the level of protein. One having ordinary skill in the art would not have been motivated to employ the immunoprecipitation assay of

Kametani et al. in the process of Bougneres et al. and, even if they did, would not have achieved the process of the instant claims. Further, one having ordinary skill in the art, in possession of the Kametani et al. reference would not have been motivated to employ the multiple step, competitive assay of Bougneres et al. because the Bourneres assay distinguishes between the presence of labeled and unlabeled protein and such a process would not have been sufficient to determine between differing forms of β -amyloid having different polypeptide chain lengths.

Endogenous β -amyloid exists in a variety of heterogeneous forms, having various polypeptide chain lengths. The Kametani et al. assay determines the relative levels of two specific forms of β -amyloid to one another through the use of antibodies to different portions of the β -amyloid protein. The Kametani et al. assay is designed to determine the ratio of β 1-42: β 1-40 because this ratio is diagnostic of patients with Alzheimer's disease. In contrast, the instant invention does not distinguish between different forms of β -amyloid but determines total β -amyloid in the sample. For example, as recited in claim 18, the β -amyloid peptide (labeled and unlabeled) is digested by a protease. As shown in the specification at paragraph [0034], this step leads to a better limit of detection in the mass spectral analysis, permitting 100-fold higher sensitivity in the mass spectrometer.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 2 TO 4 UNDER 35 U.S.C. § 103 AS OBVIOUS OVER BOUGNERES ET AL. IN VIEW OF KAMETANI ET AL. AND FURTHER IN VIEW OF SCHUTZE ET AL.

Claims 2 to 4 stand rejected under 35 U.S.C. § 103 as obvious over Bougneres et al. in view of Kametani et al., further in view of Schutze et al. Applicants traverse this rejection for the reasons provided above with regard to the rejection of claims 1, 5 to 13, 16, and 17 over Bougneres

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et al. in view of Kametani et al. Nothing in Schutze et al. cures the defect of the combination of Bourgneres et al. and Kametani et al. discussed above.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

**REJECTION OF CLAIMS 14 AND 15 UNDER 35 U.S.C. § 103 AS OBVIOUS OVER BOUGNERES ET AL.
IN VIEW OF KAMETANI ET AL. AND FURTHER IN VIEW OF NYMAN ET AL.**

Claims 14 and 15 stand rejected under 35 U.S.C. § 103 as obvious over Bougneres et al. in view of Kametani et al. and further in view of Nyman et al. Applicants traverse this rejection for the reasons provided above with regard to the rejection of claims 1, 5 to 13, 16, and 17 over Bougneres et al in view of Kamtetani et al. Nothing in Nyman et al. cures the defect of the combination of Bourgneres et al. and Kametani et al. discussed above.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

**REJECTION OF CLAIMS 18 TO 22 UNDER 35 U.S.C. § 103 AS OBVIOUS OVER BOUGNERES ET AL.,
KAMETANI ET AL., AND NYMAN ET AL., FURTHER IN VIEW OF WANG ET AL.**

Claims 18 to 22 stand rejected under 35 U.S.C. § 103 as obvious over Bougneres et al., Kametani et al., and Nyman et al., further in view of Wang et al. Applicants traverse this rejection for the reasons provided above with regard to the rejection of claims 1, 5 to 13, 16, and 17 over Bougneres et al in view of Kamtetani et al. Nothing in Nyman et al. or Wang et al. cures the defect of the combination of Bourgneres et al. and Kametani et al. discussed above.

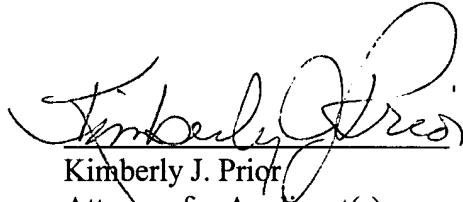
For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

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The foregoing amendment is fully responsive to the Office Action issued November 21, 2005. Applicants submit that Claims 1 to 11, 13, and 15 to 22 are allowable. Early and favorable consideration is earnestly solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney is respectfully solicited.

Respectfully submitted,



Kimberly J. Prior
Attorney for Applicant(s)
(Reg. No. 41,483)
340 Kingsland Street
Nutley, New Jersey 07110
Telephone: (973) 235-6208
Telefax: (973) 235-2363

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